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(54) Title of Invention: Imidazoline derivatives

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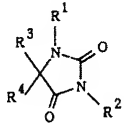
Specifications

1. Title of Invention:

Imidazolidine derivative

2. Claims:

(1) Animidazolidine derivative, shown by the general formula



[wherein R^1 is a hydrogen atom or a (lower) alkyl group which optionally has a suitable substituent,

R^2 is a lower alkyl group, lower alkylthio (lower) alkyl group, or tri-(lower) alkoxyaryl group,

R^3 is a benzyl group, and

R^4 is a lower alkyl group or an ar-(lower) alkyl group; or

R^3 is a hydrogen atom, an indolyl (lower) alkyl group which has a phenyl (C_2–C_6) alkyl group, naphthyl (lower) alkyl group, aryl group, diphenyl (lower) alkyl group, or lower alkyl group, or a dihydroindolyl (lower) alky group which has an oxo group and a lower alkyl group, and

R^4 is a hydrogen atom or lower alkyl group; provided that

If R^3 and R^4 are hydrogen atoms, R^1 is a (lower) alkyl group which optionally has a suitable substituent] and a salt thereof.

3. Detailed Explanation of the Invention:

Field of Use in Industry:

This invention concerns an imidazolidinecompound (I), which is a novel PAF (platelet activating factor) antagonist, and a salt thereof.

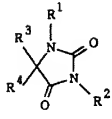
More specifically, this invention concerns a drug composition which contains an imidazolidine derivative (I) or a salt thereof as an effective ingredient, a novel imidazolidine derivative (I) and a salt thereof, and methods for producing them.

Prior Art and Problems Which the Invention Seeks to Solve:

Up to now, various compounds have been known as PAF antagonists; this invention has the purpose of developing an improved PAF antagonist.

Constitution and Effectiveness of the Invention:

The imidazolidine derivative of this invention can be shown by general formula (I) below:



(I)

[wherein R^1 is a hydrogen atom or a (lower) alkyl group which optionally has a suitable substituent,

R^2 is a lower alkyl group, lower alkylthio (lower) alkyl group, or tri-(lower) alkoxyaryl group,

R^3 is a benzyl group, and

R^4 is a lower alkyl group or an ar-(lower) alkyl group; or

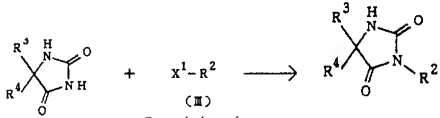
R^3 is a hydrogen atom, an indolyl (lower) alkyl group which has a phenyl (C_2–C_6) alkyl group, naphthyl (lower) alkyl group, aryl group, diphenyl (lower) alkyl group, or lower alkyl group, or a dihydroindolyl (lower) alky group which has an oxo group and a lower alkyl group, and

R^4 is a hydrogen atom or lower alkyl group; provided that

If R^3 and R^4 are hydrogen atoms, R^1 is a (lower) alkyl group which optionally has a suitable substituent].

The imidazolidine derivative (I) and salt thereof are novel compounds which can be produced by the following methods.

Production Method 1:

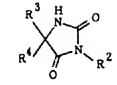


(II)
Or a salt thereof

(III)
Or a salt thereof

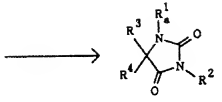
(Ia)
Or a salt thereof

Production Method 2:



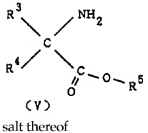
(Ia)
Or a salt thereof

+ $X^2-R^1_a$
(IV)
Or a salt thereof



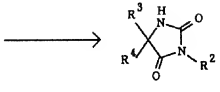
(Ib)
Or a salt thereof

Production Method 3:



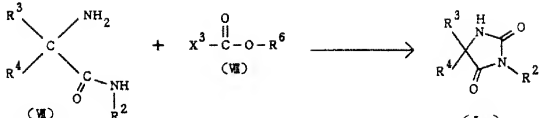
(V)
Or a salt thereof

+ $O=C=N-R^2$
(VI)
Or a salt thereof



(Ia)
Or a salt thereof

Production Method 4:



(VII)
Or a salt thereof

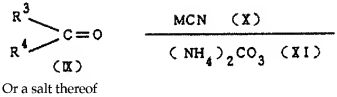
(VIII)

(Ia)
Or a salt thereof

[wherein R^1, R^2, R^3, and R^4 have the same meanings as above; X^1 is a halogen, X^2 is a halogen, R_a^1 is a (lower) alkyl group which optionally has a suitable substituent, is an esterified carboxyl group, X^3 is a halogen, and is an esterified carboxyl group].

Moreover, the raw material compound (II) can be produced by the following methods:

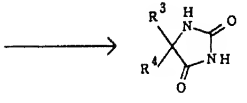
Production Method A:



(IX)
Or a salt thereof

MCN (X)

$(NH_4)_2CO_3$ (XI)



(II)
Or a salt thereof

[wherein R^3 and R^4 have the same meanings as above and M is an alkali metal].

Ideal examples of the various definitions in the descriptions given above and below in these Specifications will be discussed in detail below.

As ideal salts of the target compound (I), commonly used nontoxic salts, e.g., alkali metal salts (e.g., sodium, potassium, etc., salts), alkaline earth metal salts (e.g., calcium and magnesium salts), and salts with inorganic bases, such as ammonium salts; salts with organic bases, e.g., organic amine salts (e.g., triethylamine, pyridine, picoline,

ethanolamine, triethanolamine, dicyclohexylamine, N,N'-dibenzylethylenediamine salts, etc.); inorganic acid added salts (e.g., hydrochlorides, hydrobromides, sulfates, phosphates, etc.); organic carboxylic acid or sulfonic acid added salts (e.g., formates, acetates, trifluoroacetates, maleates, butyrates, methanesulfonates, benzenesulfonates, p-toluenesulfonates, etc.); salts with bases or acid-added salts with amino acids (e.g., aspartic acid).

"Lower" means 1–6 carbon atoms, unless otherwise specified.

Ideal "lower alkyl groups" and ideal "lower alkyl groups" in the "lower alkylthio (lower) alkyl groups," "ar-(lower) alkyl groups," "naphthyl (lower) alkyl groups," "diphenyl (lower) alkyl groups," "indolyl (lower) alkyl groups" and "dihydroindolyl (lower) alkyl groups" are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, hexyl, etc., groups.

Ideal "C_2–C_6) alkyl groups" in the "phenyl (C_2–C_6) alkyl groups" are ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, hexyl, etc., groups.

Ideal substituents in the "(lower) alkyl groups with optional suitable substituents" are, e.g., aryl groups, such as phenyl, napthyl, etc., groups; lower alkanoyl groups, suchs as formy, acetyl, propionyl, butylyl, etc., groups; carboxyl groups; carboxyl groups protected as shown below; etc.

Ideal "protected carboxyl groups" are esterified carboxyl groups, etc.; specific examples of the ester moieties of these esterified carboxyl groups are, e.g., optionally substituted lower alkyl esters, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, hexyl, etc., esters. Examples of these are lower alkanoyloxy (lower) alkyl esters, e.g., acetoxymethyl, propionyloxymethyl, butylyloxymethyl, valeryloxymethyl, pivaloyloxymethyl, 1-acetoxyethyl, 1-propionyloxyethyl, 2-propionyloxyethyl, hexanoyloxymethyl, etc., esters; lower alkanesulfonyl (lower) alkyl esters, e.g., 2-mesylethyl, etc. esters; or mono- (or di- or tri-) halo-(lower) alkyl esters, e.g., 2-iodoethyl, trichloromethyl, 2,2,2-trichloroethyl, etc., esters; lower alkenyl esters, e.g., vinyl, allyl, etc., esters; lower alkynylesters, e.g., ethynyl, propinyl esters, etc.; ar-(lower) alkyl esters which optionally have suitable substituents, e.g., benzyl, 4-methoxybenzyl, 4-nitrobenzyl, phenetyl, tolytyl, benzhydryl, bis(methoxyphenyl)methyl, 3,4-dimethoxybenzyl, 4-hydroxy-3,5-di-tertiary-butylbenzyl, etc., esters; and aryl esters which optionally have suitable substituents, e.g., phenyl, 4-chlorophenyl, tolyl, 4-tertiary-butylphenyl, xylyl, mesityl, cumenyl, etc., esters.

Ideal "aryl groups" and "aryl groups" in the "tri-(lower) alkoxyaryl" and "ar-(lower) alkyl groups" are phenyl, naphthyl, etc., groups.

Ideal "lower alkoxy groups" in the "tri-(lower) alkoxyaryl groups" are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentloxy, hexyloxy, etc., groups.

Ideal "halogens" are fluorine, chlorine, bromine, and iodine.

Ideal "esterified carboxyl groups" are those examples mentioned above.

Ideal "alkali metals" are sodium, potassium, etc.

Next, methods for producing the target compound and raw materials will be explained.

Production Method 1:

Compound (Ia) or a salt thereof can be produced by reacting compound (II) or a salt thereof with compound (III) or a salt thereof.

This reaction can be performed under the same or similar reaction conditions as those given in Working Example 1 (1) below.

Production Method 2:

Compound (Ib) or a salt thereof can be produced by reacting compound (Ia) or a salt thereof with compound (IV) or a salt thereof.

This reaction can be performed under the same or similar reaction conditions as those given in Working Example 2 (1) below.

Production Method 3:

Compound (Ia) or a salt thereof can be produced by reacting compound (V) or a salt thereof with compound (VI) or a salt thereof.

This reaction can be performed under the same or similar reaction conditions as those given in Working Example 5 (1) below.

Production Method 4:

Compound (Ia) or a salt thereof can be produced by reacting compound (VII) or a salt thereof with compound (VIII) or a salt thereof.

This reaction can be performed under the same or similar reaction conditions as those given in Working Example 6 (1) below.

Production Method A:

Compound (II) or a salt thereof can be produced by reacting compound (IX) or a salt thereof with compounds (X) and (XI).

This reaction can be performed under the same or similar reaction conditions as those given in Production Example 2 (1) below.

Target compound (I) and pharmaceutically acceptable salts thereof are antagonists of PAF; therefore, they are useful as drugs for preventing and treating diseases caused by PAF, such as allergies such as asthma, thromboses, etc.

The tests mentioned below were performed in order to show the antagonist activity of compound (I) to PAF.

Test Example (Activity of preventing platelet coagulation):

Test method:

Blood was drawn from polyethylene cannulae inserted in the carotid arteries of domestic rabbits (male Japanese white rabbits, 2.5–3 kg) and mixed with a 3.8% aqueous solution of sodium citrate (1/9 of the quantity of the blood). The blood was centrifuged at room temperature for 10 minutes, at 150 g to prepare platelet-rich plasma (PRP). Next, platelet-poor plasma (PPP) was obtained by centrifuging at 1000 g for 20 minutes. The PRP was diluted with the PPP obtained to make the platelet count 500,000/mm^3. The platelet coagulation induced by PAF was measured by measuring the changes in transmittance, by the method of Born and Cross [*Journal of Physiology*, 168 178–188 (1963)], using an NKK hemotracer (Nikko Bioscience Co.). Furthermore, the final PAF concentration in the reaction solution was made 20 nM.

Test compound:

(5R)-3-butyl-5-[(1R)-1-(1-methylindol-3-yl)ethyl]imidazolidine-2,4-dione

Test results:

IC_{50}: 1.1 μg/ml

The compound (I) or a pharmaceutically acceptable salt thereof, mixed with a pharmaceutically acceptable carrier, may be administered orally or non-orally to mammals, including human beings, in the form of a pharmaceutical composition, such as a capsule, tablet, granules, powder, oral tablet, sublingual tablet, or solution.

Examples of pharmaceutically acceptable carriers are various organic or inorganic carriers ordinarily used in drugs, including excipients, such as sucrose, starches, mannitol, sorbitol, lactose, glucose, cellulose, talc, calcium phosphate, and calcium carbonate; binders, such as cellulose, methyl cellulose, hydroxypropyl cellulose, polypropylpyrrolidone, gelatin, gum Arabic, polyethylene glycol, sucrose, starches, etc.; disintegrants, such as starches, carboxymethyl cellulose, carboxymethyl cellulose calcium salt, hydroxypropyl starch, sodium starch glycolate, sodium hydrogen carbonate, calcium phosphate, calcium citrate, etc.; lubricants, such as magnesium stearate, aerosil, talc, sodium lauryl sulfate, etc.; flavorings, such as citric acid, menthol, glycyrrhizin ammonium salt, glycine, orange powder, etc.; preservatives, such as sodium benzoate, acid sodium sulfite, methyl paraben, propylparaben, etc.; stabilizers, such as citric acid, sodium citrate, acetic acid, etc.; suspending agents, such as methyl cellulose, polyvinylpyrrolidone, aluminum stearate, etc.; dispersants, such as surface active agents; aqueous diluents, such as water; and base waxes, such as cacao fat, polyethylene glycol, white kerosene, etc.

The dose of thetarget compound varies with various factors, such as the kind of disease, the body weight and/or the age of the patient, etc., and also with the kind of administration route used.

The dose of compound (I) is ordinarily selected from the range of 1 mg–1 g/day, preferably 10–500 mg/day.

The aforementioned total dose may be divided into intervals of 6–12 hours per day.

This invention will be explained by the following production and working examples.

Production Example 1

Dicyclohexylcarbodiimide (11.8 g) was added to a mixture of N-tertiary-butoxycarbonyl-α-phenylglycine (12 g) and 3,4,5-trimethoxyanaline (8.75 g), while cooling with ice. After stirring for 15 minutes, the precipitate was filtered out. The filtrate was concentrated under a vacuum and the residue was dissolved in trifluoroacetic acid (100 ml); stirring was performed for 15 minutes at room temperature. The trifluoroacetic acid was distilled off under a vacuum and the residue was dissolved in water; the pH was adjusted to 8 with sodium hydrogen carbonate and extraction was performed with ethyl acetate. The extracted solution was concentrated under a vacuum and N-(α-phenylglycyl)-3,4,5-trimethoxyaniline (10.5 g) was obtained.

Production Example 2

(1) Dibenzylketone (5 g), potassium cyanide (3.1 g), and ammonium carbonate (11.4 g) were added to a mixture of ethanol (50 ml) and water (50 ml); stirring was performed for 8 hours at 60°C. After concentrated hydrochloric acid (8 ml) was dropped into the solution, the precipitate was filtered out, washed with water, and air-dried. 5,5-Dibenzylimidazolidine-2,4-dione (6.12 g) was obtained as a white powder.

IR (Nujol): 3300, 3200, 1755, 1720, 1700 cm^{-1}

(2) 5-(1-Phenylethyl)imidazolidine-2,4-dione

IR (Nujol): 3260, 3150, 1760, 1700 cm^{-1}

(3) 5-Benzhydryl-5-methylimidazolidine-2,4-dione

IR (Nujol): 3350, 1770, 1720 cm^{-1}

(4) 5-Benzyl-5-ethylimidazolidine-2,4-dione

IR (Nujol): 3200, 1750, 1700 cm^{-1}

Working Example 1

(1) 5-(1-Phenylethyl)imidazolidine-2,4-dione (0.34 g), potassium carbonate (1.1 g), and butyl bromide (0.46 g) were added to N,N-dimethylformamide (5 ml) and stirring was performed for 1 hour at 70°C. The solvent was distilled off under a vacuum, after which a mixture of ethyl acetate and water was added. The organic layer was poured off and dried with magnesium sulfate, after which the residue was powdered with hexane, and 3-butyl-5-(1-phenylethyl)imidazolidine-2,4-dione (0.17 g) was obtained as a white powder.

mp: 128–130°C

IR (Nujol): 3275, 1760, 1700 cm^{-1}

The following compounds were obtained in the same manner as in Working Example 1 (1).

(2) 3-Butylimidazolidine-2,4-dione

(3) 3-Butyl-5-ethyl-5-benzylimidazolidine-2,4-dione

mp: 82–83°C

IR (Nujol): 3250, 1760, 1695 cm^{-1}

(4) 3-(2-Methylthioethyl)-5-(1-naphthylmethyl)imidazolidine-2,4-dione

mp: 153–155°C

IR (Nujol): 3225, 1770, 1720 cm^{-1}

(5) 3-Butyl-5-(1-naphthylmethyl)imidazolidine-2,4-dione

mp: 118–120°C

IR (Nujol): 3220, 1765, 1715 cm^{-1}

(6) 3-Butyl-5,5-dibenzylimidazolidine-2,4-dione

mp: 153–154°C

IR (Nujol): 3325, 1755, 1710 cm^{-1}

(7) 3-Butyl-5-benzhydryl-5-methylimidazolidine-2,4-dione

mp: 141–142°C

IR (Nujol): 3330, 1775, 1700 cm^{-1}

Working Example 2

(1) 3-Butyl-5-(1-naphthylmethyl)imidazolidine-2,4-dione (0.10 g) and potassium tertiary-butoxide (45 mg) were dissolved in N,N-dimethylformamide (3 ml), and butyl bromide was added, after which stirring was performed for 10 minutes at 60°C. The solvent was distilled off under a vacuum, after which the result was purified with a silica-gel plate (ethyl acetate:hexane=1:4). 1,3-Dibutyl-5-(1-naphthylmethyl)imidazolidine-2,4-dione (90 mg) was obtained as a white powder.

mp: 57°C

IR (Nujol): 1760, 1700 cm^{-1}

The following compounds were obtained in the same manner as in Working Example 2 (1).

(2) 1-Ethoxycarbonylmethyl-3-butyl-5-(1-naphthylmethyl)imidazolidine-2,4-dione

IR (Nujol): 1760, 1705 cm^{-1}

(3) 1-Acetonyl–3-butyl-5-(1-naphthylmethyl)imidazolidine-2,4-dione

mp: 120–122°C

IR (neat): 1760, 1705 cm^{-1}

(4) 1-Isopropyl–3-butyl-5-[(1-methylindol-3-yl)methyl]imidazolidine-2,4-dione

IR (neat): 1760, 1700 cm^{-1}

(5) 1-Ethoxycarbonylmethyl–3-butyl-5-[(1-methylindol-3-yl)methyl]imidazolidine-2,4-dione

mp: 77°C

IR (Nujol): 1760, 1745, 1705 cm^{-1}

(6) 1-(1-Naphthylmethyl)–3-butyl-5-[(1-methylindol-3-yl)methyl]imidazolidine-2,4-dione

IR (neat): 1760, 1700 cm^{-1}

(7) 1-Methyl-3-butyl-5-[(1-methylindol-3-yl)methyl]imidazolidine-2,4-dione

IR (neat): 1760, 1700 cm^{-1}

(8) 1-(1-Naphthylmethyl)-3-butylimidazolidine-2,4-dione

IR (neat): 1770, 1710 cm^{-1}

(9) 1-Acetonyl-3-butyl-5-[(1-methylindol-3-yl)methyl]imidazolidine-2,4-dione

IR (neat): 1770, 1740, 1710 cm^{-1}

Working Example 3

60% Sodium hydride in oil (0.02 g) and methyl iodide (0.15 g) were added successively to an N,N-dimethylformamide (5 ml) solution of 3-butyl-5-(1-naphthylmethyl)imidazolidine-2,4-dione (0.1 g) and stirring was performed for 30 minutes at room temperature. After this, extraction was performed with water and purification was performed by thin-layer chromatography for fractionation (n-hexane:ethyl acetate=3:1) to obtain 1,5-dimethyl-3-butyl-5-(1-naphthylmethyl)imidazolidine-2,4-dione (0.027 g).

Working Example 4

A solution of (5R)-3-butyl-5-[(1R)-1-(1-methylindol-3-yl)ethyl]imidazolidine-2,4-dione (0.1 g) in water (3 ml), dioxane (3 ml), and formalin (0.5 ml) was stirred for 8 hours at room temperature; after the solvent was removed, the residue was purified by means of a silica-gel plate, and (5R)-1-hydroxymethyl-3-butyl-5-[(1R)-1-(1-methylindol-3-yl)ethyl]imidazolidine-2,4-dione (0.06 g) was obtained.

mp: 80–82°C

IR (Nujol): 3400, 1760, 1700 cm^{-1}

Working Example 5

(1) Triethylamine (1.9 ml) and butyl isocyanate (0.84 ml) were added to an N,N-dimethylformamide (20 ml) solution of methyl (2R,3R)-2-amino-3-(1-methylindol-3-yl) butyrate ester hydrochloride (1.76 g). Stirring was performed for 30 minutes at room temperature, and a 28% methanol solution of sodium methoxide was added. The mixture was stirred for 2 hours at 50°C and concentrated under a vacuum. The residue was dissolved in water (20 ml) and the pH was adjusted to 2 with concentrated hydrochloric acid, after which extraction was performed with ethyl acetate (30 ml). The extracted solution was washed with water (10 ml), dried with magnesium sulfate, and concentrated under a vacuum. The residue was purified by silica-gel column chromatography (hexane:ethyl acetate=2:1) and (5R)-3-butyl-5-[(1R)-1-(1-methylindol-3-yl)ethyl]imidazolidine-2,4-dione (60 mg) was obtained

mp: 118°C

IR (Nujol): 3250, 1760, 1700 cm^{-1}

The following compounds were obtained in the same manner as in Working Example 5 (1).

(2) 3-Butyl-5-[(1-methylindol-3-yl)methyl]imidazolidine-2,4-dione

IR (Nujol): 3280, 1740 cm^{-1}

mp: 90–91°C

(3) 3-Butyl-5-(4-chlorophenylmethyl]imidazolidine-2,4-dione

IR (Nujol): 3250, 1760, 1710 cm^{-1}

mp: 105°C

Working Example 6

Trichloromethylchloroformate (0.9 ml) was added to a toluene (10 ml) solution of N-(D-phenylalanyl)butylamine (1.61 g). Refluxing was performed for 1 hour and the result was concentrated under a vacuum. The residue was powdered with ether and (5R)-3-butyl-5-benzylimidazolidine-2,4-dione (0.39 g) was obtained.

mp: 137–138°C

IR (Nujol): 3300, 1750, 1695 cm^{-1}

The following compound was obtained in the same manner as in Working Example 6 (1).

(2) 3-(3,4,5-Trimethoxyphenyl)-5-phenylimidazolidine-2,4-dione

IR (Nujol): 3350, 1770, 1710 cm^{-1}

mp: 213–215°C

Working Example 7

A dioxane (1 ml) solution of 1-ethoxycarbonylmethyl-3-butyl-5[(1-methylindol-3-yl)methyl]imidazolidine-2,4-dione (50 mg) was added to a 10% aqueous solution of potassium hydroxide (1 ml); stirring was performed for 24 hours at room temperature, and the result was concentrated to half its quantity under a vacuum. The pH of the concentrated solution was adjusted to 1 with concentrated hydrochloric acid and extraction was performed with ethyl acetate (10 ml). The extracted solution was dried with magnesium sulfate and concentrated under a vacuum. The residue was powdered with diisopropyl ether and 1-carboxymethyl-3-butyl-5-[(1-methylindol-3-yl)methyl]imidazolidine-2,4-dione (15 mg) was obtained.

mp: 79–80°C

IR (Nujol): 3450, 1755, 1710, 1685 cm^{-1}

Working Example 8

N-bromosuccinimide (0.12 g) was added to a mixture of (5R)-3-butyl-[(1R)-1-(1-methylindol-3-yl)ethyl]imidazolidin3-2,4-dione (0.2 g) and pyridine (0.067 ml) in benzene (5 ml); stirring was performed for 2 hours. The precipitate was removed, after which the filtrate was concentrated under a vacuum. The residue was purified by thin-layer chromatography for fractionation (chloroform:methanol=10:1) and (5R)-3-butyl-5-[(1R)-1-(1-methyl-2-oxy-2,3-dihydroindol-3-yl)ethyl]imidazolidine-2,4-dione (11.3 mg) was obtained.

mp: 165–169°C

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